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WILL HEALTH CARE ECONOMIC INFORMATION LEAD TO THERAPEUTIC-CLASS WARFARE OR WELFARE?

I. INTRODUCTION

On the frontlines of the annual ninety-three billion dollar prescription drug battleground,[1] pharmaceutical companies are engaged in an increasingly fierce struggle to develop potent drugs, ensure efficient distribution chains, and seize larger market shares. The stakes are enormous: given the size of the market, "even a small share can mean large revenues."[2] In recent years, the terrain has shifted as managed care organizations (MCOs) have emerged as serious market players.[3] MCOs wield enormous influence because they determine which drugs are included on their formularies, which are "list[s] of drug products approved by the [FDA], arranged by therapeutic category, along with the reimbursement rate for the drug."[4] Formulary inclusion gives a drug manufacturer a tactical advantage over competitors within its therapeutic class.

As prescription drug costs have continued to rise,[5] MCOs have become increasingly concerned with structuring drug utilization schemes that optimize consumer health while minimizing economic expenditures. MCOs hope to reduce overall costs, even at the expense of greater short-term costs, by factoring in the costs and benefits of current health care interventions that prevent later, more expensive illnesses.[6] To do so, MCOs need health care economic information to assess the cost-effectiveness of a given drug to determine whether it should be included on the formulary.[7]

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[1] *See* Editorial, *Widen Research Funding: Medicine's Relations with Drug Firms Are Often Too Cozy*, L.A. TIMES, Feb. 21, 1998, at B7.

[2] David A. Kessler et al., *Therapeutic-Class Wars — Drug Promotion in a Competitive Marketplace*, 331 NEW ENG. J. MED. 1350, 1350 (1994).

[3] In 1996, sales to MCOs constituted over 70% of pharmaceutical revenues. *See* Stephen P. Mahinka, Kathryn L. Gleason & Kathleen M. Sanzo, *The Dominance of Managed Care Organizations as Buyers of Drugs and Medical Devices Raises Regulatory Concerns over Development and Marketing Practices*, NAT'L L.J., Sept. 15, 1997, at B4.

[4] David A. Balto, *A Whole New World?: Pharmaceutical Responses to the Managed Care Revolution*, 52 FOOD & DRUG L.J. 83, 85 (1997).

[5] *See* Andrew S. Krulwich, *The Response to Health Care Reform by the Pharmaceutical Industry*, 50 FOOD & DRUG L.J. 1, 2 (1995). Prescription drug expenditures have continued to increase with the advent of managed care. In 1996, prescription drug expenditures rose 11.7%. *See* Mahinka, Gleason & Sanzo, *supra* note 3, at B4 & n.3.

[6] Typically, researchers rely on cost-effectiveness analyses (CEAs) to compare drugs. A CEA usually "develop[s] a model of the outcomes of alternative treatments, select[s] published data on the probabilities of the outcomes to enter in the model, identif[ies] the expenses associated with each therapy, and then compar[es] the results . . . with those of various benchmark therapies." Jerome P. Kassirer & Marcia Angell, *The Journal's Policy on Cost-Effectiveness Analyses*, 331 NEW ENG. J. MED. 669, 669 (1994).

Until recently, however, FDA stifled this information.[8] Rather than adopting an economic standard for evaluating health care economic claims, FDA applied the same clinical-based standard that it used to determine drug-effectiveness.[9] Consequently, it disapproved any health care economic information that was not supported by two adequate and well-controlled studies, even if that information met what economists might conclude to be a gold standard for economic analysis. Last November, Congress addressed the issue of health care economic information within the broader context of the Food and Drug Administration Modernization Act of 1997 ("FDA Modernization Act").[10] To encourage the development of pharmacoeconomic information, Congress lowered the standard that drug manufacturers must meet to make cost-effectiveness claims.[11]

This legislative change may fan the flames of therapeutic-class warfare and lead to imperfect pharmacoeconomic information unless FDA steps in to clarify its provisions through interpretive guidelines. Part II of this Note explores the scope of the FDA Modernization Act's change with regard to health care economic information. Part III analyzes how FDA will interpret and enforce the new standard by considering how the Federal Trade Commission (FTC) has enforced a similar standard. Part IV explores the uncertain science of cost-effectiveness analysis (CEA), and Part V argues that the current provision will promote therapeutic-class warfare because it fails to address methodological shortcomings in CEA. Part VI then offers three complementary solutions, followed by a brief conclusion in Part VII.

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[7] This Note uses the terms "health care economic" and "pharmacoeconomic" interchangeably.

[8] *See* Peter J. Neumann, Darren E. Zinner & A. David Paltiel, *The FDA and Regulation of Cost-Effectiveness Claims*, HEALTH AFF., Fall 1996, at 54, 59–60. These authors note:

> [Randomized controlled trials] have long been the gold standard by which the FDA judges the safety and efficacy of new drugs. Moreover, use of economic analyses alongside clinical trials may produce more reliable estimates. However, imposing such a requirement on cost-effectiveness analysis likely will create a higher standard of evidence than what is needed.

Id. (footnote omitted).

[9] *See id.* at 57.

[10] Pub. L. No. 105-115, 111 Stat. 2296 (1997).

[11] *See id.* § 114.

II. SCOUTING THE TERRAIN — THE NEW LEGAL FRAMEWORK FOR HEALTH CARE ECONOMIC INFORMATION

A. *FDA's Jurisdiction over Pharmaceuticals*

FDA derives its authority from the Federal Food, Drug, and Cosmetic Act ("FD&C Act").[12] The FD&C Act authorizes FDA to regulate any food, drug, device, or cosmetic that is intended for, actually in, or delivered through interstate commerce, or is held thereafter for sale, to ensure that it has not been "adulterated" or "misbranded."[13] It gives FDA the authority to require an application for any new drug that is "not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling"[14] prior to its introduction in interstate commerce.[15] Conversely, FDA exercises only general police power to monitor the advertising of regulated drugs.[16] However, FDA has piggy-backed on its authority to regulate labeling by adopting the enforcement position that advertising must reflect labeling, which is subject to premarket approval.[17]

B. *FDA's Approach Prior to the FDA Modernization Act*

Prior to the enactment of the FDA Modernization Act, FDA regulated the provision of health care economic information with the same stringency that it devoted to regulating the safety and effectiveness of new drugs.[18] Just as pharmaceutical companies had to present "substantial evidence" of safety and effectiveness to gain FDA approval for a new drug,[19] FDA required pharmaceutical companies to demonstrate

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[12] 21 U.S.C. §§ 301–395 (1994).

[13] *See id.* § 331. This misbranding provision serves as the basis for FDA's authority to regulate the advertising of prescription drugs. Since 1962, FDA has relied on the new drug approval process for its jurisdiction to regulate labeling. *See* Thomas A. Hayes, *Drug Labeling and Promotion: Evolution and Application of Regulatory Policy*, 51 FOOD & DRUG L.J. 57, 61 (1996).

[14] 21 U.S.C. § 321(p)(1).

[15] *See id.* § 355(a).

[16] *See id.* § 352(n). Prior to 1962, FTC was responsible for policing advertising of both over-the-counter and prescription drugs. However, Congress amended the FD&C Act in 1962 to make FDA responsible for prescription drug advertising after congressional testimony "revealed serious abuses in advertising to the medical profession." *See* Hayes, *supra* note 13, at 61.

[17] Typically, FDA issues a warning letter when it finds a violation. *See, e.g.*, FDA, FDA's Electronic Freedom of Information Reading Room: Warning Letters (last visited 5/6/98) <http://www.fda.gov/foi/warning.htm> (providing a search engine to locate Letter from Minnie Baylor-Henry, Director, Division of Drug Marketing, Advertising, and Communications, to Richard U. De Schutter, Chairman, President and CEO, G.D. Searle & Co. (Nov. 21, 1997)).

[18] In 1962, Congress rejected relative efficacy as a criterion and chose objective effectiveness. *See* PETER BARTON HUTT & RICHARD A. MERRILL, FOOD AND DRUG LAW 478 (2d ed. 1991).

[19] 21 U.S.C. § 355(d). The Act defines "substantial evidence" as follows:

> [T]he term . . . means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and

"substantial evidence" or "substantial clinical evidence" prior to making any cost-effectiveness claims.[20] FDA recodified its policy to consider cost-effectiveness claims within its misbranding provisions in 1976: "Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug . . . ."[21] Although a few companies submitted the requisite two adequate and well-controlled studies and ultimately gained approval to make specific pharmacoeconomic claims, many opted to forego this route — because of time and cost concerns — in favor of alternative marketing strategies. Thus, due to FDA's restrictive approach to cost-effectiveness claims, the development and dissemination of health care economic information languished.

C. *Congress's New Approach*

Congress recognized the importance of health care economic information to MCOs when it considered the FDA Modernization Act.[22] Having identified this need, Congress responded by including a health care economic provision in the FDA Modernization Act.[23] This provision defines "health care economic information" to mean "any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention."[24]

> responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed . . . in the labeling . . . .

Id. FDA typically interpreted this term to require a minimum of two adequate and well-controlled investigations. *See* H.R. REP. NO. 105-310, at 67 (1997). However, in the context of new drug approvals, the FDA Modernization Act shifted the presumption to a requirement of only one adequate and well-controlled study plus confirmatory evidence. *See id.*

[20] S. REP. NO. 105-43, at 42 (1997). FDA promulgated regulations to support this interpretation:

> An advertisement . . . is false, lacking in fair balance, or otherwise misleading . . . if it . . . [c]ontains a drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience.

21 C.F.R. § 202.1(e)(6)(ii) (1997).

[21] 41 Fed. Reg. 6907, 6908 (1976) (recodifying 21 C.F.R. § 201.6(a)).

[22] The Senate Committee on Labor and Human Resources noted, "[f]or years, sophisticated users of health[-]related economic information . . . have been constrained from access to important information that could help them reduce health-care costs." S. REP. NO. 105-43, at 3 (1997).

[23] *See* Pub. L. No. 105-115, § 114, 111 Stat. 2296, 2312 (1997). The Act declared:

> Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug and is based on competent and reliable scientific evidence.

Id. § 114(a).

[24] *Id.*

Congress lowered the standard of proof that a manufacturer must meet to substantiate health care economic claims. Under the new framework, Congress now only requires pharmaceutical companies to base health care economic claims on "competent and reliable scientific evidence."[25] Not surprisingly, this new standard is largely context-driven: "the nature of the evidence required to support various components of health care economic analyses depends on which component of the analysis is involved."[26]

Although it relaxed the standard of proof, Congress explicitly limited who can receive health care economic information. This information can be disseminated to formulary committees, MCOs, and other similar entities; however, individual physicians are excluded.[27] Unlike MCOs, which are capable of considering health care economic information through an expert deliberative process, individual physicians typically lack the necessary skills and time to weigh the relevant merits of health care economic claims.[28] "This limitation is important because it will ensure that the information is presented only to parties who have established procedures and skills to interpret the methods and limitations of economic studies."[29]

Congress also limited potential health care economic claims to already approved drug uses. Specifically, health care economic information provided by pharmaceutical companies will not be considered a false, misleading, or illegal new drug claim as long as it "directly relates to an [approved] indication,"[30] as reflected in the approved physician package insert. This section explicitly prohibits drug manufacturers from making any pharmacoeconomic claims relating to unapproved uses of an approved drug. For example, "economic claims based on preventing disease progression would ordinarily not be considered to be directly related to an approved indication for the treatment of symptoms of a disease, for a drug for which the use in prevention of disease progression has not been approved."[31]

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[25] *Id.* Of course, drug manufacturers are still obligated to establish the safety and efficacy of new drugs with substantial evidence. *See* S. REP. NO. 105-43, at 43 (1997).

[26] H.R. REP. NO. 105-310, at 66–67 (1997). The Committee offers several illustrations:

> [M]odeling the resource savings of insulin therapy to achieve tight control of blood sugar in Type 1 diabetes could include cost savings associated with the prevention of retinopathy (an eye disease) and nephropathy (kidney disease), based on well-controlled study(ies) that demonstrate that control of blood sugar levels with insulin leads to a reduction of such consequences. Because prevention of retinopathy and nephropathy could not simply be assumed to be a result of blood sugar control, these prevention claims would have to be shown by well-controlled study(ies) before inclusion as health care outcome assumptions.
>
> In contrast, economic claims that model, based on observational studies in a population of women, the economic consequences of prevention of fractures due to osteoporosis would be permitted for drugs already approved for prevention of fractures due to osteoporosis. This is possible because observational data may be considered competent and reliable for making an assumption about the secondary consequences of an osteoporotic fracture once the primary prevention has been established.

Id. at 66.

[27] *See* FDA Modernization Act § 114(a).

[28] *See* H.R. REP. NO. 105-310, at 65 (1997).

[29] *Id.*

[30] FDA Modernization Act § 114(a).

Lastly, Congress used this provision to change the default rule for health care economic claims from a requirement of prior approval to one of permissive publication. As noted above, FDA required drug manufacturers to gain premarket approval of any health care economic claim — if it was used in labeling — before publicizing it. Although FDA's current postmarketing reporting regulations still require drug manufacturers to submit health care economic information to FDA at the time such information is initially provided to a formulary committee or other managed care provider, drug manufacturers are now allowed to market their claims immediately.[32]

III. PULLING OUT FDA PEACEKEEPERS — WHO WILL POLICE HEALTH CARE ECONOMIC CLAIMS UNDER THE NEW LAW?

Because the health care economic provision within the FDA Modernization Act did not go into effect until February 19, 1998,[33] FDA has yet to articulate its approach to implementing the new "competent and reliable scientific evidence" standard for health care economic information.[34] In making the standard for health care economic claims more lenient, Congress expressly equated this new standard with FTC's long-standing reasonable basis requirement.[35] Thus, an analysis of FTC's interpretation and enforcement of its reasonable basis standard may illuminate FDA's likely approach.

A. *Interpreting the Standard*

Adopted in 1984, FTC's standard states that "a firm's failure to possess and rely upon a reasonable basis for objective claims constitutes an unfair and deceptive act or practice in violation of section 5 of the Federal Trade Commission Act."[36] Rather than relying on a rigid test, FTC utilizes a flexible, multifactor approach to evaluate the accuracy of advertising claims.[37] When specifically confronted with comparative scientific claims, FTC tends to define "competent and reliable scientific evidence" as "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."[38] Thus, FTC's approach suggests that FDA may adopt a contextual approach that allows for variation in the type of evidence that can be used to substantiate a cost-effectiveness claim.

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[31] H.R. REP. NO. 105-310, at 66 (1997). The Committee illustrated its explanation: "rheumatoid arthritis drugs are approved for the treatment of symptoms and not for the prevention of deformity. Therefore economic claims based in part on an assumption of prevention of deformity would not be considered directly related to the approved indications for these drugs." *Id.*

[32] *See id.* at 67.

[33] The FDA Modernization Act stated that this provision would take effect 90 days after enactment, which occurred on November 21, 1997. *See* FDA Modernization Act § 501.

[34] FDA plans to issue draft guidelines in the near future to explain how it will interpret this new standard. *See FDA Pharmacoeconomics Guidance Expected After April*, F-D-C REP. ("The Pink Sheet"), Feb. 23, 1998, at 6, 6 (noting that "FDA will not complete a draft guidance . . . until at least April"). FDA will publish this guidance for the standard 60-day notice and comment period. *See id.*

[35] The Senate Committee on Labor and Human Resources was clear on this point: "[This] legislation would apply the Federal Trade Commission's 'competent and reliable scientific evidence' standard for FDA review of health care economic statements . . . ." S. REP. NO. 105-43, at 3 (1997). A report by the House Committee on Commerce observed that the FTC standard "takes into account the current scientific standards for assessing the various types of data and analyses that underlie such information." H.R. REP. NO. 105-310, at 66 (1997).

B. *Enforcing the Standard*

FTC leverages its regulatory power by relying on private enforcement mechanisms.[39] Individuals, companies, and consumer organizations frequently promote FTC's regulatory goals by initiating private lawsuits against false or misleading advertisers. Section 43(a) of the federal Lanham Trade-Mark Act provides a private cause of action against companies whose advertisements are either false or likely to result in consumer confusion.[40] The shift to private enforcement is one of the most significant changes in the new health care economic provision. Although rival drug manufacturers were not precluded from suing under the Lanham Trade-Mark Act even if FDA found that a pharmacoeconomic claim had a substantial basis, in reality the complaining drug manufacturer would have had virtually no chance of overcoming the presumption of legitimacy afforded by FDA approval. Now, the lower standard and lack of premarket approval may provide fertile ground for private actions between rival drug manufacturers, which would allow FDA to capitalize on the self-interest of rival pharmaceutical companies to enforce its regulatory standards. This reliance on private enforcement enables FDA to preserve limited resources and still meet competing objectives.[41]

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[36] FTC Policy Statement Regarding Advertising Substantiation Program, 49 Fed. Reg. 30,999, 31,000 (1984).

[37] *See id.* "These factors include: the type of claim, the product, the consequences of a false claim, the benefits of a truthful claim, the cost of developing substantiation for the claim, and the amount of substantiation experts in the field believe is reasonable." *Id.*

[38] *E.g.*, *In re* Metagenics, Inc., *available in* 1997 FTC LEXIS 313, at *12–*13 (Oct. 31, 1997) (finding in a consent decree that the defendant lacked a reasonable basis for claiming that its product, Bone Builder, prevents bone loss, bone thinning, or osteoporosis).

[39] *See* Janet D. Steiger, Commissioner, Federal Trade Commission, Remarks at the Practicing Law Institute Conference (Sept. 17, 1996), *in False Advertising and the Law: Coping with Today's Challenges*, WEST LEGAL NEWS, Nov. 25, 1996.

[40] *See* 15 U.S.C. § 1125(a) (1994). This section provides:

> Any person who, on or in connection with any goods or services, or any container for goods, uses in commerce any . . . false or misleading representation of fact, which . . . in commercial advertising or promotion, misrepresents the nature, characteristics, qualities, or geographic origin of his or her or another person's goods, services, or commercial activities, shall be liable in a civil action by any person who believes that he or she is or is likely to be damaged by such act.

Id. In a case involving competing hypertension drugs, Miles, Inc. successfully counterclaimed against Pfizer, Inc. for a preliminary injunction by demonstrating a sufficient likelihood of success at trial on its claim that Pfizer had promoted comparative advertisements that were literally false. *See* Pfizer, Inc. v. Miles, Inc., 868 F. Supp. 437, 460 (D. Conn. 1994).

IV. HIGH-TECH WEAPONRY — THE UNCERTAIN SCIENCE OF CEA

The trend towards managed care — with its concomitant battle to contain costs while preserving the quality of care — has fueled the demand for accurate health care economic information.[42] Although the FDA Modernization Act explicitly defines the output of CEA, it fails to address methods that will be used to generate that output.[43] The wide disparity in methods currently used to conduct CEA[44] renders the resulting pharmacoeconomic information suspect. A recent survey of MCO decisionmakers found that they considered current health care economic information only "moderately useful" in making drug purchasing decisions,[45] although they ascribed a much higher value to the future usefulness of such information.[46] In an attempt to account for this disparity between the potential benefits of health care economic information and the more disappointing reality, the remainder of this Part explores the shortcomings of the current approach to CEA.

One problem that arises from the use of divergent methodologies is the way that researchers identify and calculate the relevant costs that should be included in the numerator of the cost-effectiveness ratio. Although economic theory dictates that a "change in the use of a resource caused by its health intervention should be valued at its opportunity cost,"[47] researchers have had a hard time applying this theory in practice.[48] A similar host of problems confronts researchers trying to identify and calculate the relevant benefits that should be included in the denominator of the cost-effectiveness ratio. A comprehensive cost-benefit analysis would weigh all of the benefits accruing to society, even if those benefits do not accrue directly to the MCO. Yet, researchers know that MCOs have an incentive to discount purely societal benefits.[49] Furthermore, researchers have struggled to express these benefits in a meaningful way. One scientific panel suggested incorporating these health benefits variables into a standard unit of measurement called "quality-adjusted life-years" (QALYs).[50] However, "[t]here are a number of methodologic challenges involved in estimating QALYs, including: how to classify health states; whose preferences to use in judging the desirability of the health states; how to measure preferences; and how to adjust for time preferences."[51]

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[41] Even before the enactment of the FDA Modernization Act, FDA's elimination of its preclearance requirement for general marketing information caused an increase in the number of complaints from both rival companies and internal sources. *See FDA's New View of Drug Promotion: FDLI Meeting*, PHARMA MARKETLETTER, Sept. 22, 1997, at 12, 13.

[42] *See* Brian McCann, *Poor Studies Giving Bad Name to Pharmacoeconomic Research*, DRUG TOPICS, Apr. 21, 1997, at 52, 52 ("In this era of economic pressures in health care, there's an urgent need for good pharmacoeconomic studies."). A recent study found that MCO decisionmakers desire more "'health outcomes-oriented' comparative studies . . . that compare rival therapies and drug brands." *Marketing Smart: What Makes Your MCO Tick?*, PHARMACEUTICAL EXECUTIVE, Mar. 1997, at 54, 60 [hereinafter *Marketing Smart*].

[43] For the most part, Congress did not pay much attention to these types of concerns. Senator Paul D. Wellstone was one of the few who questioned the underlying scientific basis of health care economic information in the Committee Report. "[H]ealth economics is not an exact science as individual variations and circumstances are very important when considering treatment. There is a great danger in extrapolating from the whole population to a specific patient." S. REP. NO. 105-43, at 5 (1997) (remarks of Sen. Paul Wellstone, separately published in an errata).

[44] *See* Kessler et al., *supra* note 2, at 1352 ("[T]here is still no consensus on how to conduct cost-effectiveness studies.").

[45] *Marketing Smart*, *supra* note 42, at 60. When asked to rank the usefulness of pharmacoeconomic studies on formulary development on a scale from 1 (lowest) to 10 (highest), the mean response was 5.48, with a standard deviation of 2.53. *See id.* at 60 tbl.

[46] The mean response was 7.81, with a standard deviation of 1.79. *See id.*

Even if researchers accurately identify and measure the health care costs and benefits associated with a given treatment, three other sources of uncertainty remain. First, researchers must estimate the effectiveness of given treatment interventions. "The quality and validity of a CEA depend crucially on the quality of the underlying data that describe the effectiveness of interventions and the course of illness without intervention."[52] Typically, researchers develop a model based on primary and secondary data sources to estimate effectiveness. On a primary level, researchers might rely on studies conducted specifically to inform the CEA.[53] On a secondary level, researchers might rely on reports of randomized controlled trials, observational studies, uncontrolled experiments, or descriptive series.[54] However, FDA's previous position that "effects need to be demonstrated by adequate and well-controlled studies" rather than simply estimated through "meta-analyses, assumptions[,] or expert opinion" posed a serious obstacle to the development of workable models.[55] It is unclear whether, or how, FDA will alter its treatment of modeling assumptions under the new law. In addition, the new statute only allows consideration of approved drug uses, not off-label uses, even if the latter represent the medical standard of care.

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[47] Milton C. Weinstein et al., *Recommendations of the Panel on Cost-Effectiveness in Health and Medicine*, 276 JAMA 1253, 1255 (1996).

[48] For instance, should researchers include health care costs that result solely from the fact that a successfully treated patient will live longer and will therefore encounter other health problems? Should researchers distinguish between those later health costs that occur due to intervention and those that are unrelated to the treatment intervention? *See id.* at 1255–56.

[49] *See* Neumann, Zinner & Paltiel, *supra* note 8, at 65 ("[M]any studies are conducted from a societal perspective, even though managed care plans are concerned with their own perspectives.").

[50] Weinstein et al., *supra* note 47, at 1254.

[51] Peter J. Neumann, Darren E. Zinner & Janice C. Wright, *Are Methods for Estimating QALYs in Cost-Effectiveness Analyses Improving?*, 17 MED. DECISION MAKING 402, 403 (1997). This study concluded that more rigor and consistency were needed in the estimation of QALYs. *See id.* at 407.

[52] Weinstein et al., *supra* note 47, at 1257.

[53] *See id.* However, some researchers question whether a randomized clinical trial is appropriate because the high quality of participating clinicians, the relative health of enrolled patients, and the greater attention to detail may skew the predictive outcome of CEA in favor of the treatment. *See* P.M. Fayers & D.J. Hand, *Generalisation from Phase III Clinical Trials: Survival, Quality of Life, and Health Economics*, THE LANCET, Oct. 4, 1997, at 1025, 1025.

Second, researchers must incorporate consistent discount rates and time preferences. In calculating the cost-effectiveness ratio of a treatment, researchers must calculate the net present value of the costs and benefits. One problem that arises in this calculation is that CEAs frequently incorporate different discount rates that hamper cross-study comparisons.[56] Another, less obvious problem occurs when researchers fail to discount all costs and benefits equally. "Discounting the value of future expenditures requires that health effects experienced in the future also be discounted at the same rate. . . . Failure to discount health effects will lead to inconsistent choices over time."[57] These problems stem from relatively elementary causes but still pose obstacles to cross-study comparisons.

Third, some CEAs fail to address the uncertainty that results from their dependence on a multitude of frequently debatable assumptions. "Cost-effectiveness analyses are subject to uncertainty with regard to estimates of effectiveness, the course of illness, [health-related quality-of-life] consequences and preferences, and health care utilization and costs."[58] Depending on the nature of the assumption and the relative importance of the variable, health care economic outcomes can be significantly affected. However, some studies fail to incorporate appropriate sensitivity analyses that would place the relevant assumptions in an understandable context.[59]

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[54] *See* Weinstein et al., *supra* note 47, at 1257.

[55] *FDA Pharmacoeconomic Guidance to Reflect "Needs of Managed Care," Agency Says*, F-D-C REP. ("The Pink Sheet"), Jan. 12, 1998, at 15, 15 (quoting Laurie Burke, epidemiologist, Division of Drug Marketing, Advertising & Communications, FDA) (internal quotation marks omitted) [hereinafter *FDA Pharmacoeconomic Guidance*]; *see also* Neumann, Zinner & Paltiel, *supra* note 8, at 60 (noting that FDA's previous guidelines treated modeling unfavorably, and gave grudging acceptance to its use "only if well-controlled trials [were] not available").

[56] *See* Weinstein et al., *supra* note 47, at 1257 (noting that "a wide variety of discount rates are used in the literature and can be defended").

[57] *Id.*

[58] *Id.*

[59] *See FDA Pharmacoeconomic Guidance*, *supra* note 55, at 16.

V. EDGING TOWARD THE BRINK — THE THREAT OF CLASS WARFARE

The free market, by itself, is not likely to address completely these methodological shortcomings. This Part begins by analyzing the potential for bias under the new framework and the likelihood that pharmaceutical companies might use lower-quality health care economic information to gain an advantage. It then considers whether market forces are strong enough to establish a workable framework for health care economic information.

A. *The Potential for Bias*

The new framework for health care economic information leaves in place the existing incentives for bias and also exacerbates the incentive for researchers to make biased assumptions. First, researchers are still required to make numerous, often subtle assumptions in order to develop workable models. Because most CEAs are done for marketing purposes,[60] "the assumptions made in constructing the models and the data used in the analysis . . . could be biased."[61] The *New England Journal of Medicine* described a few examples of the tangled web of financial arrangements:

> [W]e recently saw an analysis for which an author received money directly from the company, another in which the author had a patent pending on an application described in the report, and another in which an author was a consultant to the company that markets the drug that was studied. . . . Certainly the financial arrangements created an incentive for bias.[62]

In short, there is no guarantee that researchers — directly paid, indirectly paid, or even unpaid — will remain objective.[63]

Second, the new framework provides added incentives for bias. The lower standard of proof — competent and reliable scientific evidence — suggests that researchers can afford to make some of the questionable assumptions that they may have been reluctant to make under the stricter standard. Thus, this new standard may actually increase the number of low-quality studies that purport to offer conclusive health care economic information. One expert's observation of CEAs under the former standard is revealing: "There are very few well-done pharmacoeconomic studies in the literature; many are quick and dirty studies done for marketing and promotion. They are beginning to denigrate and give a bad name to the research area."[64] Even if the lower standard will not exacerbate existing incentives for bias, it does nothing to ameliorate these incentives.

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[60] In a survey of pharmaceutical industry executives, 69% said that they conducted pharmacoeconomic studies for use in product promotion or positioning. *See U.S. Players View Health/Pharmacoeconomic Studies*, PHARMA MARKETLETTER, Mar. 3, 1997, at 14, 14.

[61] Kassirer & Angell, *supra* note 6, at 669.

[62] *Id.*

[63] *See generally* Joan Stephenson, *Medical Journals Turn Gaze Inward to Examine Process of Peer Review*, 278 JAMA 1389, 1389–91 (1997) (describing some of the most pernicious kinds of bias in peer review); *Morning Edition* (CNN television broadcast, Jan. 8, 1998), *available in* 1998 WL 3305985 (indicating that 96% of scientists who wrote in favor of certain blood pressure drugs had financial links to the drug companies that supplied those drugs, compared to 37% of critics).

B. The Role of Market Forces

Market forces will ameliorate some, but not all, of the incentives to produce low-quality pharmacoeconomic information. Specifically, drug manufacturers, pharmaceutical organizations, and MCOs have incentives to provide or demand high-quality economic information. For instance, a manufacturer of a cost-effective drug can distinguish its product by submitting the CEA for publication in a peer review journal. Journals would effectively screen CEAs for the highest quality studies, and then give those studies their endorsement by publishing them.[65] Although not every CEA would be sufficiently thorough and unbiased, MCOs would have a pool of high-quality, published studies from which to select drugs for their formulary lists.

However, the failure of peer review journals to discover or disclose potential sources of bias somewhat attenuates this private sector solution. Several years ago, the *New England Journal of Medicine* confronted the issue of possible bias in CEAs submitted for publication.[66] The *Journal* announced its policy that a CEA would be excluded if any of its authors had a conflict of interest.[67] However, the *Journal*'s

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[64] McCann, *supra* note 42, at 52 (quoting Stephen Schondelmeyer, a professor at the University of Minnesota's College of Pharmacy) (internal quotation marks omitted). Dr. Peter Neumann has suggested an alternate, albeit admittedly less likely, possibility: pharmaceutical companies may actually be more cautious in making economic claims because those claims are based on models of long-term costs and benefits, and the legislative history explicitly prohibits the inclusion of benefits that derive from unapproved uses of a given drug. *See* Telephone Interview with Dr. Peter J. Neumann, Assistant Professor of Policy and Decision Sciences, Harvard School of Public Health (Mar. 3, 1998); *see also* H.R. REP. NO. 105-310, at 65–66 (1997). For instance, "economic claims based on prolonging patient survival would not be considered directly related and would not, therefore, be permitted under this subsection for agents approved for the symptomatic treatment of heart failure, but not approved for prolonging survival in heart failure patients." *Id.* at 66.

[65] *See* Peter J. Neumann & Darren E. Zinner, *Evaluating and Regulating Pharmacoeconomic Information in the Private Sector*, 32 DRUG INFO. J. 525, 529 (1998).

[66] *See* Kassirer & Angell, *supra* note 6, at 669. The *Journal* observed:

> [Formal cost-effectiveness analyses] are similar to original articles in that the methods and data are explicit and the conclusions are based on the data presented. Yet, they are like review articles in that the assumptions made in constructing the models and the data used in the analysis are usually chosen selectively from the literature, and the choices could be biased.

Id.

[67] *See id.* CEAs must meet the following requirements:

> [A]ny study supported by industry must be funded by a grant to a not-for-profit entity such as a hospital or a university, not to an individual or group of individuals. We will not review such studies if any of the authors is receiving a direct salary from the sponsoring company or a competing company, or if any author has an equity interest in, an ongoing

enforcement record on non-CEA studies has been less than exemplary. Recently, the *Journal* "published a scathing review of an environmental book — but failed to identify the reviewer as director of medicine and toxicology at W.R. Grace & Co., one of the nation's largest chemical manufacturers and one of two corporations linked to the leukemia cluster in Woburn, Mass."[68] This and other failures cast doubt on the premise that peer review journals are thoroughly able to investigate potential sources of bias in CEAs.

The peer review process itself may fail to detect significant errors. One study of the peer-review process deliberately introduced eight errors into a test manuscript. None of the reviewers caught all eight errors, and few caught more than two or three.[69] This detection problem might be exacerbated if researchers deliberately try to hide the weaknesses of their research.[70] Thus, exclusive reliance on peer review journals to legitimate CEAs appears misplaced.

Besides relying on the peer review process, individual pharmaceutical companies have self-help alternatives to deter junk CEAs. For instance, the Lanham Trade-Mark Act[71] provides a solid cause of action for drug companies whose products have been falsely or confusingly portrayed; however, the high cost of trademark litigation diminishes the Act's effectiveness. Similarly, companies can publish sharp attacks on junk CEAs to reaffirm the cost-effectiveness of their products.

Market incentives may also encourage pharmaceutical organizations to take a more active role in policing health care economic claims. In 1995, the Pharmaceutical Research and Manufacturers of America developed a set of pharmacoeconomic principles to guide CEAs.[72] Given the current state of CEAs, these efforts to establish industry-wide standards do not appear to have had a significant impact. However, commentators have already begun to explore numerous other private models that might supplement or replace government regulation, such as watchdog/adjudication systems, accreditation, seals

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> consultancy with, or membership on the scientific advisory board of such a company, or a related patent pending.

Id.

[68] Nancy Evans, *Ethical Questions Prompted by Medical Journal Review*, TIMES UNION (Albany), Feb. 10, 1998, at D3 (describing several failures to disclose potential sources of authors' bias). Similarly, the *New England Journal of Medicine* "published an editorial last year claiming that the benefits of diet drugs outweigh the risks of heart damage, without saying that its authors were paid consultants for companies that made or marketed one of those drugs, Redux." *Widen Research Funding: Medicine's Relations with Drug Firms Are Often Too Cozy*, *supra* note 1, at B7.

[69] *See* Stephenson, *supra* note 63, at 1391.

[70] *Cf. id.* at 1390 ("Many authors are also guilty of leaving out information that does not support their conclusions ...." (quoting John C. Bailar III, of the University of Chicago) (internal quotation marks omitted)).

[71] 15 U.S.C. § 1125(a) (1994).

[72] *See* Neumann & Zinner, *supra* note 65, at 529 & n.11.

of approval, rating systems, and peer review journals.[73] Although these private models hold potential, they also entail significant antitrust concerns and substantial transition costs.

Another possibility is that MCOs will require pharmaceutical companies to submit high-quality health care economic information to qualify for formulary consideration. Although the low quality of junk CEAs may not be readily apparent, MCOs have institutional memories that will allow them to respond accordingly in later iterations. However, other market forces might lead some MCOs to defect from this strategy of requiring high-quality pharmacoeconomic information. For instance, drug manufacturers might fall back on other considerations already in use — such as bundling, pharmaceutical benefits managers, or volume discounts — to compensate for the low quality of economic information. Finally, MCOs are not monolithic; although many MCOs are extremely sophisticated, others may not be sophisticated enough to exert comparable pressure or conduct effective analysis of economic information.[74]

Market forces may not be able to correct the lack of cross-study comparability that currently exists among studies that rely on highly divergent methodologies. First, individual MCOs will be reluctant to invest the time and resources necessary to devise a "reference case" — a set of standard assumptions and approaches that, when incorporated into every CEA, facilitates cross-study comparisons[75] — because the benefit produced from devising a reference case is outweighed by the cost involved for any individual MCO. Even if an individual MCO were willing and able to invest the time and resources, it would still be faced with an enforceability problem — namely, drug manufacturers who fail to meet the reference case requirements might simply peddle their wares elsewhere. Furthermore, even if the pharmaceutical industry or some professional society were to agree to require adherence to a given reference case, there would be no enforcement mechanism to punish individual companies that defect from the group strategy.

Given that exclusive reliance on market forces is unlikely to redress completely the methodological shortcomings of many CEAs, FDA should step in to facilitate the development of CEA standards. However, FDA must not be too restrictive in addressing economic assumptions that can be used in modeling, lest it continue to stifle the economic information that is most important to MCOs. Although these assumptions of effectiveness may tangentially promote unauthorized drug uses, FDA's fears should be alleviated because this information only flows to sophisticated purchasers, not individual prescribers, and appears in the overall context of a CEA. With the understanding that FDA should tolerate some economic assumptions of effectiveness, the next Part offers three complementary suggestions that may help to ameliorate the problems of bias and cross-study comparability discussed above.

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[73] *See id.* at 527–29.

[74] *Compare Managed Care Can Police Pharmacoeconomic Promotions, Lilly Exec Claims*, F-D-C REP., INC. ("The Pink Sheet"), Jan. 12, 1998, at 17, 17 ("If a company makes a false or misleading claim, managed care . . . is going to find out very rapidly and the penalty for that is exclusion from formulary which is a fate far worse than any government regulator can impose." (quoting Tim Franson, Vice President of Research and Regulatory, Lilly Corporation) (internal quotation marks omitted)), *with FDA Pharmacoeconomic Guidance*, *supra* note 55, at 16 ("Many managed care groups do not really know what their information needs are. . . . They lack management information systems, they lack integrated pharmacy medical claims, they lack the skills and expertise to actually make evaluations to put into practice disease management protocols." (quoting Paul Langley, Managed Care Pharmacy Representative, University of Colorado Health Sciences Center) (internal quotation marks omitted)).

[75] *See* Weinstein et al., *supra* note 47, at 1253.

VI. NEGOTIATING AN ARMISTICE — WORKABLE SOLUTIONS TO REAL-WORLD PROBLEMS

The former system of strict FDA regulation stifled pharmacoeconomic information and failed to ensure unbiased health care economic information that could serve as the basis for cross-study comparison. If FDA is to succeed in promoting health care economic information, it must combine its regulatory guidance with its reliance on the free market. Nonetheless, FDA's inability to promote high-quality health economic information under the prior framework should not prevent it from stepping in now. Although FDA's former micro-level approach was fairly effective at guaranteeing the reliability of CEAs that received approval, it missed the proverbial forest for the trees — widely disparate, but individually accurate assumptions underlying most CEAs significantly undermined the basis for cross-study comparison.[76] FDA should adopt a more macro-level approach to facilitate the growth of health care economic information. Three complementary options include requiring a set of "reference case" assumptions, enacting mandatory financial disclosure requirements, and requiring explanation of all significant assumptions.

A. *Promulgating Reference Case Assumptions*

One controversial and partial solution to the problems of bias and comparability would be for FDA to require pharmaceutical companies making health care economic claims to include a reference case, defined by a standard set of assumptions and methods, within every CEA. "While an investigator might also present results based on different methods and assumptions to serve the other purposes of the analysis, the reference case serves as a point of comparison across studies."[77]

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[76] *See id.* ("The divergence of methods used to conduct [CEA] interferes with the ability of decision makers charged with resource allocation to make appropriate comparisons of cost-effectiveness (C/E) ratios across programs.").

The Panel on Cost-Effectiveness in Health and Medicine has already laid most of the groundwork for this option.[78] Sponsored by the United States Public Health Service, this nonfederal panel — consisting of experts in CEA, clinical medicine, ethics, and health outcomes measurement — developed methodological and reporting recommendations designed to improve the quality and comparability of cost-effectiveness studies.[79] The Panel's final product was a 1996 reference case. The Panel recommended conducting the reference case from a societal perspective in which "[h]ealth effects include both benefits and harms, even when these occur in people who are not the intended recipients of the intervention."[80] The Panel endorsed the societal perspective because it "never counts as a gain what is another party's loss."[81] In addition, the Panel recommended using QALYs in order to measure health effects.[82] The Panel felt that these general approaches, along with more technical details,[83] would be most effective at guaranteeing cross-study comparability.

Although the reference case recommendations have yet to be implemented on a systematic basis, this option offers several advantages. First, it would not require FDA to expend a tremendous amount of resources. Once FDA promulgates a reference case, it could then depend on individuals, rival companies, and consumer organizations to help police health care economic claims. Thus, FDA could conserve its resources for those occasions when it receives credible notice of a violation. Second, this option enhances the cross-comparability of studies by narrowing the range of heretofore divergent methodologies. Finally, it establishes a baseline for CEAs that will compel researchers to utilize more reliable economic models.

However, this option is not costless. Although a societal perspective may increase comparability, it may not be the most useful format for MCOs, which are more concerned with their individual bottom lines.[84] Although researchers would be free to incorporate other assumptions in separate cases, they would have to follow the reference case. Second, there are inherent uncertainties in measuring quality-of-life considerations that preclude anything approaching absolute precision.[85] Finally, establishing a fixed reference case may stultify development of more advanced techniques of economic analysis.

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[77] Louise B. Russell et al., *The Role of Cost-Effectiveness Analysis in Health and Medicine*, 276 JAMA 1172, 1173 (1996).

[78] *See* Weinstein et al., *supra* note 47, at 1253.

[79] *See id.* The panel explained:

> [The recommendations were based on] a number of considerations, including economic and decision theory; consistency in the accounting of costs and consequences; ethical concerns; pragmatic concerns; and the needs of users of analyses. In some instances, where neither theory nor these other considerations led to a clear choice, the panel recommended a conventional practice for the sake of consistency across studies.

Id. at 1254.

[80] Russell et al., *supra* note 77, at 1174.

[81] *Id.*

[82] *See id.* at 1175.

[83] For a detailed explanation of more technical issues in CEA, consult Weinstein et al., cited above in note 47, at 1253, which explains the methodology for determining components belonging in a cost-effectiveness ratio, measuring costs, valuing health consequences, estimating effectiveness of interventions, establishing time preference and discounting, and handling uncertainty.

B. *Enacting Mandatory Financial Disclosure Requirements*

Another option is for FDA to enact mandatory financial disclosure requirements for researchers conducting CEAs. Under this option, researchers would be required to disclose all financial ties that they might have with a given pharmaceutical company or drug product to every recipient of health care economic information. This option accords with FDA's recently proposed financial disclosure rules for clinical trial investigators.[86] The final rule, which is scheduled to go into effect on February 2, 1999, requires sponsors to disclose whether any clinical investigators held a proprietary interest in the product under consideration, maintained a significant equity investment in the sponsor of the study (in excess of $50,000), or received a significant payment from the sponsor (in excess of $25,000).[87]

This mandatory disclosure requirement for CEA researchers does not go as far as the *New England Journal of Medicine*'s conflict-of-interest policy, which categorically disqualifies any CEA in which the author has a personal financial interest.[88] However, it does require that researchers bring these ties into the sunlight, and thereby enables MCOs to apply the necessary amount of skepticism to health care economic claims. This option recognizes that "[c]omplete disclosure and more rigorous review seem more reasonable than an outright ban on coauthors with a direct financial stake, since good ideas and good research can come from investigators regardless of funding sources."[89]

C. *Requiring Explanation of All Significant Assumptions*

A third complementary option would require researchers to disclose every significant assumption that was made in deriving economic claims. MCOs, as sophisticated end-users, could then evaluate this information in light of the relevant assumptions and formulate their own informed comparisons. Although MCOs probably would not be able to compare the claims in their initial form, the disclosure of assumptions would operate as the key to unlock the study, explore its contours, and ultimately facilitate comparability.

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[84] *See* Neumann, Zinner & Paltiel, *supra* note 8, at 65.

[85] *See* Neumann, Zinner & Wright, *supra* note 51, at 402.

[86] *See* 63 Fed. Reg. 5233 (1998). Specifically, FDA's proposed rule does not prohibit clinical trial investigators from having financial interests, but does mandate that FDA be made aware of these relationships when it evaluates the clinical data used to support drug, device, and biologics marketing applications. *See id.* at 5235.

[87] *See id.* at 5233, 5237.

[88] *See* Kassirer & Angell, *supra* note 6, at 669.

[89] Peter J. Neumann, *Paying the Piper for Pharmacoeconomic Studies*, 18 MED. DECISION MAKING S23, S25 (1998) (supplement to Vol. 18, No. 2).

Mandatory disclosure offers several advantages. For example, it allows researchers to target their CEAs for the relevant audience, in this case MCOs. Instead of deriving relatively more complicated estimates of social costs and benefits that may be ignored, researchers can supply the bottom-line information that MCOs demand most. In addition, this option does not lock in the current state of technology, but allows models to adapt as new techniques are developed.

However, this option also entails costs. First, FDA must define what constitutes a "significant" assumption that must be flagged and explained for the customer. Although FDA could require researchers to identify and explain every assumption that they make in their analysis, this requirement would almost certainly prove to be too unwieldy for MCOs (who only need to know the significant assumptions). Preferably, FDA should respond to this problem by providing a nonexhaustive list (similar to the reference case categories) of assumptions that must be disclosed, coupled with a more general standard requiring disclosure of, for example, "all other factors or assumptions that would be reasonably necessary to evaluate health care economic information." Second, individual studies would not be immediately comparable because they would still be based on different assumptions and methodologies. Thus, MCOs would still have to invest resources to examine these CEAs and formulate a basis for comparison.

VII. CONCLUSION

CEA offers an important tool for addressing the two growing concerns in health care — cost containment and quality of care. By enabling MCOs to compare various treatment interventions, health care economic information can help maximize social welfare as well as MCOs' profitability. Unfortunately, the current state of CEA — with its potential for bias and lack of comparability across studies — may be more conducive to promoting therapeutic-class warfare than social welfare. As this Note demonstrates, the new approach to health care economic information embodied in the FDA Modernization Act may actually increase the potential for misuse of health care economic information. Consequently, FDA should facilitate the development of market mechanisms by adopting a set of reference case assumptions, mandatory financial disclosure requirements, and mandatory explanations of significant assumptions. By doing so, FDA will lend guidance to drug companies and researchers engaged in CEA, and will provide MCOs with usable, accurate health care economic information.